

**Prequalification Unit Inspection services**  
**WHO PUBLIC INSPECTION REPORT**  
**(WHOPIR)**

**Desk Assessment of Active Pharmaceutical Ingredient (API) Manufacturer**

<b>Part 1</b>	<b>General information</b>
<b>Company information</b>	
Name of Manufacturer	Almelo Pvt Ltd
Corporate address of manufacturer	8-2-120/45/N2, Lane Opp.: Mayfair Apartments, Road No: 2, Banjara hills, Hyderabad -50003, Telangana, India.
<b>Inspected site</b>	
Name & address of manufacturing site	Almelo Pvt. Ltd., Unit-11, Survey No: 227, 228 & 136, 137, Shabashpally Village, Shivampet Mandai, Medak District- 502334, Telangana, India.
Synthetic Unit/Block/Workshop	Unit-11
<b>Desk assessment details</b>	
Date of review	30 May – 25 July 2022
APIs covered by this desk assessment	APIMF453 Dolutegravir Sodium WHOAPI453 Dolutegravir Sodium
List of documents submitted	<ol style="list-style-type: none"> <li>A list of all regulatory inspections performed in the last 5 years and their outcomes</li> <li>The full inspection reports, including deficiency letters, for inspections performed by a competent stringent regulatory authority in the past 5 years</li> <li>Proof of CAPA implementation and final decision by the competent stringent regulatory authority related to observations or deficiencies noted in the latest inspection report or to any warning letter or equivalent regulatory action</li> <li>A copy of the manufacturing authorization and GMP certificate granted by the local national authority</li> <li>A site master file whose approval date was not more than one year ago, and any forecast modifications, together with legible colour printouts of water treatment and air-handling systems, including pipeline and instrumentation drawings in A3 or A2</li> <li>The list of all the API manufactured on-site.</li> <li>The most recent product quality review (PQR) of the concerned product covering all required subsections and trend results, including statistical evaluation.</li> </ol>

	<ul style="list-style-type: none"> <li>h. The completed batch manufacturing and packaging records, including the analytical part, for the most recently released batch of relevant product.</li> <li>i. The list of any recalls in the past three years related to any product manufactured on site with quality defects.</li> <li>j. A confirmation by the senior quality assurance representative that a full self-inspection or external audit dedicated to the product has been performed and all matters dealt with.</li> <li>k. Master batch manufacturing and packaging records of the WHO product of interest</li> <li>l. A copy of any warning letter, or equivalent regulatory action, issued by any authority to which the site provides or has applied to provide the product</li> <li>m. Description of any recent or foreseen out-of-stock situations</li> </ul>	
<b>Part 2</b>	<b>Summary of SRA/NRA inspection evidence considered (from most recent to last)</b>	
<i>National Institute of Pharmacy and Nutrition, Hungary OGYEI</i>	Dates of inspection:	19-22.11.2018
	Type of inspection:	Initial inspection
	Block/Unit/Workshop:	Large Size Production Area (Manufacturing Block A)
	APIs covered:	Pregabalin CAS 148553-50-8 Ranolazine CAS 95635-55-5
<b>Part 3</b>	<b>Summary of the last WHO inspection</b>	
Not applicable. The site has never been inspected by WHO		
<b>Abbreviations</b>	<b>Meaning</b>	
BMR	Batch manufacturing record	
BPR	Batch production record	
CAPA	Corrective and preventive action	
CC	Change control	
GMP	Good manufacturing practices	
NC	Non conformity	
NRA	National regulatory agency	
PQR	Product quality review	
PQS	Pharmaceutical quality system	
QA	Quality assurance	
QC	Quality control	
QCL	Quality control laboratory	
QMS	Quality management system	
QRM	Quality risk management	
RA	Risk assessment	
RCA	Root cause analysis	

SOP	Standard operating procedure
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<b>Part 4</b>	<b>Summary of the assessment of supporting documentation</b>
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**a) Manufacturing authorization and GMP certificate granted by the local authority:**

The company provided a copy of the manufacturing license issued by the Drugs Control Administration (DCA)-Government of Telangana including a list of 63 APIs that could be manufactured under Form 25 and 2 APIs that could be manufactured under Form 28.

The most recent GMP certificate issued by the Drugs Control Administration-Government of Telangana, following an inspection was also provided.

**b) Site master file (SMF):**

The company provided the most recent version of the SMF

The QMS principles are summarized in the SMF and are in accordance with GMP, ICHQ7 and Schedule M.

The site is located approximately 60Km north of Hyderabad and it is surrounded by fields. The facilities were constructed in 2017. According to the layout the site consists of the following areas/buildings:

Manufacturing Block A

Manufacturing Block B

Utility Block

Almelo House (Administration, QA, RA and QC laboratories)

RM Warehouse

FG Warehouse

Solvent Tank Farm

Boiler

ETP

Canteen

Scrap Yard

According to the company clean rooms have clear divisions of Wet Material, Dry Material and Powder processing area. They are supplied with clean air via AHUs which are maintained and qualified.

Layouts of the facilities (including clean areas), the HVAC system and the water system are included in the SMF. The layouts of the HVAC system and the water system did not give rise to any comments.

**c) List of all the APIs or other products (intermediates, dosage forms) manufactured on-site:**

The company provided a list of APIs that are currently manufactured on site.

It is noted that Dolutegravir Sodium is not included in the Form 25 and Form 28 lists of products.

**d) List of all regulatory inspections performed in the last 5 years and their outcomes:**

The company has been inspected by four different authorities in the last five years and all inspections indicated that the site was GMP compliant.

**e) Most recent product quality review(s) (PQR)(s) of the concerned WHO API(s):**

The company provided the Dolutegravir Sodium PQR. No batches were manufactured during the review period (January 2021 to December 2021).

Review of the 12-month hold time studies in accelerated conditions for the intermediates indicated that there was no significant change or adverse trend.

With regards to the finished product, five batches were placed in accelerated conditions and the 6-month results indicate that the API is stable. Similarly, the same batches were placed in long term and Zone IV B stability studies and the 12-month results indicate that the API is stable. During analysis of a stability sample an OOS was registered which was due to a technical error. Appropriate CAPA were applied. No complaints were registered during the review period

**f) Batch manufacturing and packaging record(s), including the analytical part, for the most recently released batch of relevant API(s):**

Batch manufacturing records of the intermediates were provided. Some minor discrepancies in batch record entries were identified. These discrepancies should be discussed during the next on-site inspection.

In addition, the BMR of Dolutegravir Sodium API was provided. Dimethylformamide is used to clean and rinse some of the manufacturing equipment. The use of dimethylformamide as a rinsing agent should be discussed at the next inspection in relation to the potential risk of N-Nitrosamine formation.

Analytical records for intermediates and finished product were provided. Review of these records did not give rise to any comments.

**g) Master batch manufacturing and packaging record(s) of the API(s) of interest:**

Master batch records for intermediates and Dolutegravir finished product were provided. These Master BMRs were created for Dolutegravir validation batches. No unique identification numbers were assigned to master BMRs.

**h) Recalls in the past three years related to APIs with quality defects:**

The company provided a statement confirming that no recalls have taken place until the application for desk assessment was submitted.

**i) Confirmation by the senior quality assurance representative that a full self-inspection or external audit dedicated to the API(s) has been performed and all matters dealt with:**

A statement was provided by the General Manager of Quality Assurance that periodic internal review of the products and Almelo facilities are performed to ensure the status of compliance is maintained for all quality systems

**j) Copy of any warning letter, or equivalent regulatory action, issued by any authority for their market, to which the site provides or has applied to provide the API(s):**

The company confirmed that no warning letters have been issued by any regulatory authorities against the site until the application for desk assessment was submitted.

**k) Out-of-stock situations:**

According to the company no out-of-stock situations were observed in recent times for any of the APIs manufactured. Additionally, the company does not foresee any such situation in near future.

<b>Part 5</b>	<b>Conclusion – Desk assessment outcome</b>
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Based on the GMP evidence received and reviewed, it is considered that a desk assessment is acceptable in lieu of a WHO onsite inspection. The site *Almelo Pvt. Ltd. Unit II* located at *Survey No: 227, 228 & 136, 137, Shabashpally Village, Shivampet Mandai, Medak District- 502334, Telangana, India* is considered to be operating at an acceptable level of compliance with WHO GMP guidelines for APIs.

This compliance status shall be valid until August 2023 or when another inspection is conducted by WHO or by a stringent regulatory authority

<b>Part 6</b>	<b>List of guidelines referenced in this inspection report</b>
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1. WHO good manufacturing practices for active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 2. **Short name: WHO GMP for APIs or WHO TRS No. 957, Annex 2**  
<http://apps.who.int/medicinedocs/documents/s20119en/s20119en.pdf>
2. WHO good manufacturing practices for pharmaceutical products: main principles. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-eighth Report Geneva, World Health Organization, 2014 (WHO Technical Report Series, No. 986), Annex 2. **Short name: WHO TRS No. 986, Annex 2**  
[http://www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/expert\\_committee/trs\\_986/en/](http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_986/en/)
3. WHO good manufacturing practices: water for pharmaceutical use. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fourth-sixth Report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 2. **Short name: WHO TRS No. 970, Annex 2**  
[http://www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/expert\\_committee/trs\\_970/en/](http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_970/en/)
4. WHO guidelines for sampling of pharmaceutical products and related materials. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninth Report. Geneva, World Health Organization, 2005 (WHO Technical Report Series, No. 929), Annex 4. **Short name: WHO TRS No. 929, Annex 4**  
[http://whqlibdoc.who.int/trs/WHO\\_TRS\\_929\\_eng.pdf?ua=1](http://whqlibdoc.who.int/trs/WHO_TRS_929_eng.pdf?ua=1)
5. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 8. **Short name: WHO TRS No. 1010, Annex 8**  
[http://www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/expert\\_committee/trs\\_1010/en/](http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_1010/en/)

6. Supplementary guidelines on good manufacturing practices: validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth Report. Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 4.  
**Short name: WHO TRS No. 937, Annex 4**  
[http://whqlibdoc.who.int/trs/WHO\\_TRS\\_937\\_eng.pdf?ua=1](http://whqlibdoc.who.int/trs/WHO_TRS_937_eng.pdf?ua=1)
7. WHO Good Practices for Pharmaceutical Quality Control Laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957, Annex 1).  
**Short name: WHO TRS No. 961, 957), Annex 1**  
<http://www.who.int/medicines/publications/44threport/en/>
8. WHO Good Practices for Pharmaceutical Products Containing Hazardous Substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fourth Report. Geneva, World Health Organization, 2010 (WHO Technical Report Series, No. 957), Annex 3.  
**Short name: WHO TRS No. 957, Annex 3**  
<http://www.who.int/medicines/publications/44threport/en/>
9. WHO good manufacturing practices for sterile pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 6.  
**Short name: WHO TRS No. 961, Annex 6**  
[http://whqlibdoc.who.int/trs/WHO\\_TRS\\_961\\_eng.pdf?ua=1](http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1)
10. WHO guidelines on transfer of technology in pharmaceutical manufacturing WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 7.  
**Short name: WHO TRS No. 961, Annex 7**  
[http://whqlibdoc.who.int/trs/WHO\\_TRS\\_961\\_eng.pdf?ua=1](http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1)
11. Model guidance for the storage and transport of time-and temperature-sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 9.  
**Short name: WHO TRS No. 961, Annex 9**  
[http://whqlibdoc.who.int/trs/WHO\\_TRS\\_961\\_eng.pdf?ua=1](http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1)
12. General guidelines for the establishment maintenance and distribution of chemical reference substances. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-first Report Geneva, World Health Organization 2007 (WHO Technical Report Series, No.943) Annex 3.  
**Short name: WHO TRS No. 943, Annex 3**  
[http://whqlibdoc.who.int/trs/WHO\\_TRS\\_943\\_eng.pdf?ua=1](http://whqlibdoc.who.int/trs/WHO_TRS_943_eng.pdf?ua=1)



13. WHO good practices for pharmaceutical microbiology laboratories. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 2.  
**Short name: WHO TRS No. 961, Annex 2**  
[http://whqlibdoc.who.int/trs/WHO\\_TRS\\_961\\_eng.pdf?ua=1](http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1)
14. WHO guidelines on quality risk management. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 2. **Short name: WHO TRS No. 981, Annex 2**  
[http://www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/expert\\_committee/trs\\_981/en/](http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/)
15. WHO guidelines on variation to a prequalified product. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh Report Geneva, World Health Organization, 2013 (WHO Technical Report Series, No. 981), Annex 3. **Short name: WHO TRS No. 981, Annex 3**  
[http://www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/expert\\_committee/trs\\_981/en/](http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/trs_981/en/)
16. WHO guidelines for drafting a site master file. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth Report Geneva, World Health Organization, 2011 (WHO Technical Report Series, No. 961), Annex 14. **Short name: WHO TRS No. 961, Annex 14**  
[http://whqlibdoc.who.int/trs/WHO\\_TRS\\_961\\_eng.pdf?ua=1](http://whqlibdoc.who.int/trs/WHO_TRS_961_eng.pdf?ua=1)
17. WHO Guidelines on good manufacturing practices: validation, Appendix 7: non-sterile process validation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 3. **Short name: WHO TRS No. 992, Annex 3**  
[http://www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/expert\\_committee/WHO\\_TRS\\_992\\_web.pdf](http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf)
18. WHO General guidance on hold-time studies WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 4. **Short name: WHO TRS No. 992, Annex 4**  
[http://www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/expert\\_committee/WHO\\_TRS\\_992\\_web.pdf](http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf)
19. WHO Technical supplements to Model Guidance for storage and transport of time – and temperature – sensitive pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 5. **Short name: WHO TRS No. 992, Annex 5**  
[http://www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/expert\\_committee/WHO\\_TRS\\_992\\_web.pdf](http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf)

20. WHO Recommendations for quality requirements when plant – derived artemisinin is used as a starting material in the production of antimalarial active pharmaceutical ingredients. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-ninth Report Geneva, World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 6  
**Short name: WHO TRS No. 992, Annex 6**  
[http://www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/expert\\_committee/WHO\\_TRS\\_992\\_web.pdf](http://www.who.int/medicines/areas/quality_safety/quality_assurance/expert_committee/WHO_TRS_992_web.pdf)
21. Guidance on good data and record management practices. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 5.  
**Short name: WHO GDRMP guidance or WHO TRS No. 996, Annex 5**  
[http://www.who.int/medicines/publications/pharmprep/WHO\\_TRS\\_996\\_annex05.pdf](http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf)
22. WHO general guidance on variations to multisource pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fiftieth Report. Geneva, World Health Organization, 2016 (WHO Technical Report Series, No. 996), Annex 10.  
**Short name: WHO Multisource guidance or WHO TRS No. 996, Annex 10**  
[http://www.who.int/medicines/publications/pharmprep/WHO\\_TRS\\_996\\_annex10.pdf](http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf)
23. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 10.  
**Short name: WHO TRS No. 1010, Annex 10**  
[http://www.who.int/medicines/publications/pharmprep/WHO\\_TRS\\_996\\_annex10.pdf](http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex10.pdf)
24. Production of water for injection by means other than distillation. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 3.  
**Short name: WHO TRS No. 1025, Annex 3**  
<https://www.who.int/publications-detail/978-92-4-000182-4>
25. Good chromatography practice. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 4.  
**Short name: WHO TRS No. 1025, Annex 4**  
<https://www.who.int/publications-detail/978-92-4-000182-4>
26. Points to consider for manufacturers and inspectors: environmental aspects of manufacturing for the prevention of antimicrobial resistance. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-fourth Report. Geneva, World Health Organization, 2020 (WHO Technical Report Series, No. 1025), Annex 6.  
**Short name: WHO TRS No. 1025, Annex 6**  
<https://www.who.int/publications-detail/978-92-4-000182-4>



27. WHO guidance on good practices for desk assessment of compliance with good manufacturing practices, good laboratory practices and good clinical practices for medical products regulatory decisions. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fifty-second Report. Geneva, World Health Organization, 2018 (WHO Technical Report Series, No. 1010), Annex 9. **Short name: WHO TRS 1010, Annex 9**  
[https://www.who.int/medicines/areas/quality\\_safety/quality\\_assurance/TRS1010annex9.pdf?ua=1](https://www.who.int/medicines/areas/quality_safety/quality_assurance/TRS1010annex9.pdf?ua=1)